SPIRONOLACTONE-INDUCED AGRANULOCYTOSIS: A CASE REPORT

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A 43-year-old woman with liver cirrhosis and hepatocellular carcinoma was admitted for the chief problem of ascites. Laboratory data revealed a leukocyte count of 3.8×10^9/L on the second day of admission. Spironolactone was prescribed for diuresis beginning on the third day. Routine blood tests on the tenth day disclosed marked leukopenia (1.8×10^9/L). Four days later, the leukocyte count was still 1.8×10^9/L and a differential count revealed agranulocytosis (neutrophils, 0.25×10^9/L). Eight days after withdrawal of spironolactone, the leukocyte count returned to normal (leukocytes, 4.9×10^9/L; neutrophils, 1.76×10^9/L). On review of the patient's clinical condition, concurrent medication, and previous reports, we highly suspected that this episode of agranulocytosis was caused by spironolactone. Unlike four previously reported cases, this one did not involve furosemide, which is reported to be associated with leukopenia and agranulocytosis.

Key Words: spironolactone, agranulocytosis
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Drugs are the most common cause of agranulocytosis [1]. Furosemide has been reported to be highly associated with drug-induced agranulocytosis in a population-based case-control study [2]. However, only four cases of spironolactone-induced agranulocytosis have been previously reported [3–6], all of which were concurrently treated with furosemide. Here, we report a case of spironolactone-induced agranulocytosis. To the best of our knowledge, this is the first case of spironolactone-induced agranulocytosis without concurrent furosemide therapy.

CASE PRESENTATION

A 43-year-old woman refused chemotherapy after being diagnosed with hepatocellular carcinoma. She underwent transarterial embolization 3 months before being admitted to the National Cheng Kung University Hospital, Taiwan, on November 19, 2002, for ascites. Jaundice had been noted for 2 months before admission. Lower abdominal pain with distension, poor appetite, and oliguria had developed in the 2 weeks prior to presentation. No nausea, vomiting, or weight loss was observed. Due to the deterioration in her general condition, she was admitted for further management. Her vital signs were stable: blood pressure, 98/64 mmHg; heart rate, 86 beats/minute; and temperature, 37°C.

Laboratory tests on November 20 revealed the following: leukocytes, 3.8×10^9/L; platelets, 8.9×10^9/L; hemoglobin, 11.7 g/dL; blood urea nitrogen, 8.0 mg/dL; and creatinine, 0.5 mg/dL. Liver function tests showed total bilirubin, 3.9 mg/dL; aspartate aminotransferase, 135 U/L; alanine aminotransferase, 71 U/L; and albumin, 3.4 g/dL.

The only medication being taken on admission was silymarin. Tramadol, which was prescribed intermittently for pain during the past 4 months, was also added on November 20. Spironolactone 12.5 mg tid was given to control the ascites from November 21; the dose was increased to 25 mg tid 2 days later. On November 24, her leukocyte count was 2.6×10^9/L, platelets were 7.2×10^9/L, and the white blood cell differential count (WBC-DC) showed

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segments, 77.9%; eosinophils, 1%; basophils, 0.1%; monocytes, 1.1%; and lymphocytes, 19.9%. On November 28, her leukocyte count was 1.8×10^9/L, platelets were 23.3×10^9/L, and segments were 49.0%.

The exact cause of leukopenia was not identified immediately. However, because an episode of bleeding esophageal varices developed, the doctor withdrew the spironolactone and tramadol on December 1. The next day, her leukocyte count was 1.8×10^9/L; platelets, 19.0×10^9/L; segments, 13.9%; monocytes, 23.0%; and lymphocytes, 58.1%. On December 5, her leukocyte count was 1.9×10^9/L and platelet count was 19.7×10^9/L, and WBC-DC showed promyelocytes, 1%; myelocytes, 2%; metamyelocytes, 1%; bands, 3%; segments, 1%; basophils, 6%; monocytes, 32%; and lymphocytes, 51% (manual count). On December 9, the leukocyte count returned to 4.9×10^9/L and the platelet count to 18.3×10^9/L, and the WBC-DC showed myelocytes, 4%; metamyelocytes, 2%; bands, 22%; segments, 36%; basophils, 2%; monocytes, 14%; and lymphocytes, 19% (manual count). The time course for spironolactone administration, leukocyte counts, and granulocyte counts are shown in the Figure. The concurrent medication during this period included a supply of intravenous branched chain amino acids, tramadol, somatostatin, and terlipressin.

The patient did not receive filgrastim during her hospitalization. On review of the disease, the patient's medication, and previous reports, we highly suspected that spironolactone was the cause of this episode of agranulocytosis.

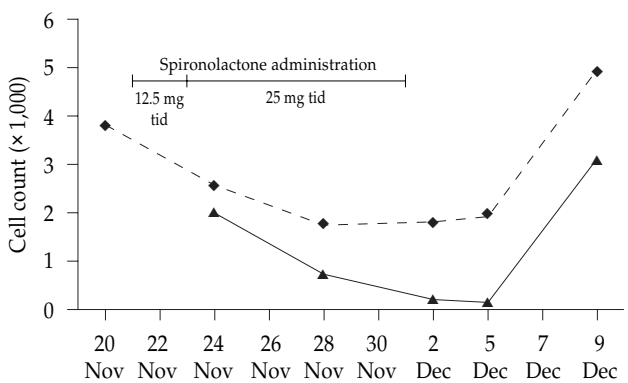

Figure. *Time course of spironolactone administration, white blood cell count (◆), and absolute neutrophil count (▲).*

Discussion

The diagnosis of agranulocytosis in this case was certain from the decrease in granulocytes (absolute neutrophil count, ANC, decreased to < 500 cells/mm^3) after admission to the normalization of the granulocyte counts with a left shift later in the serial tests of the complete blood count and WBC-DC. Acute neutropenia only occurs in a few clinical diseases [1], and drugs are considered to be the most common cause [1].

No remarkable clinical event in this patient could have contributed to the neutropenia. She was not given any chemotherapy for the carcinoma. In addition, she and her family denied taking any other preparations, except the prescribed medications in our hospital. Therefore, we highly suspected that her medication after admission was the cause of this neutropenia. In view of the clinical course after the withdrawal of medication, the disappearance of the neutropenia, and a review of the literature [3–6], we considered spironolactone to be the cause of this neutropenia.

In this case, amino acids were given from November 20 to 28 for nutritional support. Somatostatin and terlipressin were started on November 29 when leukopenia was observed. Somatostatin was not withdrawn until December 9. Amino acids, somatostatin, and terlipressin are all unlikely causes of this episode of agranulocytosis. Tramadol was given from November 20 to December 1. Withdrawal of spironolactone and tramadol on December 1 was followed by a normalization of the patient's white cell count on December 9. Tramadol had often been used to control the patient's abdominal pain without any adverse reaction and has not been reported to be associated with agranulocytosis. Of the drugs withdrawn, only spironolactone was newly instituted and is reported to cause agranulocytosis in the medical literature.

In this case, agranulocytosis was noted during routine follow-up of the blood cell count and no specific symptoms were apparent. Once an adverse reaction is suspected, discontinuance of the suspected drug followed by disappearance of the adverse reaction is presumptive evidence of a drug-induced illness. Confirmatory evidence may be sought by re-introducing the drug to see if the reaction reappears. As the adverse effect of agranulocytosis is life-threatening, re-challenge is not preferred for ethical reasons. According to Naranjo et al's adverse drug reaction algorithm [7], the total agranulocytosis score in this patient was 7, which is categorized as "probable".

The mechanisms by which neutropenia develops after drug administration include decreased production of

Table. Comparison of reported cases in the medical literature

Parameters	Stricker & Oei	Jivraj et al	Ferguson et al	Whitling et al	Hsiao et al
Age (yr)	70	57	65	58	43
Gender	F	M	F	F	F
Spironolactone dose	100 mg qd	25 mg q6h	Not reported	200 mg qd, 100 mg qn	25 mg tid
Furosemide dose	80 mg qd	80 mg bid	Not reported	20 mg bid	Not combined
Onset	5 wk	4 d	8 d	30 d	7 d
Leukocytes ($\times 10^3/mm^3$)	2.6	2.3	1.64	1.0	1.8
Neutrophils ($\times 10^3/mm^3$)	0	0.14	0.1	0.01	0.25
Recovery	7 d	14 d	5 d	5 d	10 d
Bone marrow biopsy	Myelocytes, absence of mature granulocytes	Normal cellularity	Not done	Myeloid hypoplasia	Not done
Concurrent medications	Digoxin	Domperidone, prochlorperazine, digoxin, warfarin	Amoxicillin, digoxin, captopril, verapamil	Glipizide, lactulose, multivitamins	Tramadol, amino acids, somatostatin, terlipressin
Diagnosis	CHF, renal failure	CHF, severe rheumatic heart disease, ventricular arrhythmias	CHF, atrial fibrillation, pleural effusion	Cryptogenic hepatic cirrhosis	Hepatic cirrhosis, hepatocellular carcinoma

F = female; M = male; CHF = congestive heart failure.

stem cells and immune-mediated peripheral destruction. Drug toxicity due to the first mechanism is usually dose-related and dependent on continued administration. Damage to stem cells or a granulocytic precursor in the bone marrow prevents differentiation of granulocytes, without affecting the peripheral pool of neutrophils. Immune-mediated neutropenia, on the other hand, usually develops within 7 days of exposure [1]. The bone marrow tries to compensate for the peripheral destruction of neutrophils and typically has a normal or hypercellular appearance.

In the report by Stricker and Oei [4], a bone marrow biopsy revealed many myelocytes and an absence of mature granulocytes, supporting a direct toxic effect of the drug on the bone marrow. However, the patient reported by Jivraj et al had normal cellularity in the bone marrow [3], suggesting peripheral destruction of circulating leukocytes. The clinical manifestation in our case seems to favor peripheral destruction of neutrophils. Nonetheless, the mechanism for spironolactone-induced agranulocytosis should be further clarified.

Our case shows a similar clinical presentation to that reported by Jivraj et al (Table). However, our case is the only one of the five reported that did not involve furosemide, which is also reported to be associated with leukopenia and agranulocytosis [2].

In summary, we have reported a case of agranulocytosis secondary to spironolactone administration without furosemide therapy in a patient with liver cirrhosis complicated by hepatocellular carcinoma. We propose that leukocyte counts be monitored for the first month of spironolactone therapy.

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